REMARKS

Claims 18-33 are pending in the application with claim 18 being the sole independent claim. Claims 29-33 have been withdrawn as being directed to a non-elected invention in the restriction election filed June 4, 2007. Claim 18 has been amended to correct the chemical structure to include a methyl group at the C13 position, so that the structure corresponds with the specification and the elected species 1,3,5(10)-estratien-3,15,16,17-tetrol. Support for this amendment can be found in the originally filed specification at page 8, lines 20+. The Abstract has been amended similarly to correct this chemical structure. A clean copy of the amended Abstract is attached.

Claim 18 has also been amended to remove the phrase "when used in the present method" as suggested by the Examiner.

Claim 18 has further been amended to change the term "preventing" to prophylactically treating. Support for this amendment can be found in the specification on page 13, lines 3-4.

Lastly, claim 18 has been amended to eliminate the following immune mediated disorders: insulin dependent diabetes (type I diabetes); systemic lupus erythrematosis; psoriasis; immune pathologies induced by infectious agents, viral infections or bacterial infections; tuberculosis, lepromatous leprosy; transplant rejection; graft versus host disease; atopic conditions; eosinophilia; conjunctivitis and glomerular nephritis

No new matter has been added.

ARGUMENTS

Rejection under 35 U.S.C. §112, second paragraph:

Claims 18-28 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Examiner's rejection with respect to claim 18 has been addressed above. Accordingly, it is respectfully requested that the rejection of claims 18-28 under 35 U.S.C. §112, second paragraph, be withdrawn.

With respect to the rejection of claim 28 under 35 U.S.C. §112, second paragraph, the Examiner objects to the additionally claimed disease "multiple sclerosis" recited in this claim because claim 18 failed to initially recite this disease. The Examiner's attention is directed to page 14, line 7 of the specification which lists multiple sclerosis as one of several autoimmune diseases. Base claim 18 recited a method of treating immune mediated disorders in a mammal wherein the immune mediated disorder is selected from the group consisting of autoimmune diseases. This recitation of "autoimmune diseases" in claim 18 would encompass multiple sclerosis as listed in dependent claim 28. In any event, claim 18 has now been amended to recite "multiple sclerosis". Accordingly, it is respectfully requested that the rejection of claim 28 under 35 U.S.C. §112, second paragraph, be withdrawn.

Rejection under 35 U.S.C. §112, first paragraph:

Claims 18-28 are rejected under 35 U.S.C. §112, first paragraph, as failing to provide an enabling disclosure. It is the Examiner's position that the specification is enabling for treating an immune mediated disease as defined in claim 18, but does not reasonably provide enablement for preventing such immune mediated diseases. Page 9 of the Office Action specifically states "Therefore, currently there is no known method that can truly prevent the development of immune mediated disease by employing a single therapeutic estrogenic agent because the causes of these diseases are either still unknown or derived from diverse factors". In response thereto, claim 18 has been amended to state a method of treating or preventing an immune mediated disease selected from the group consisting of multiple scleroris, rheumatoid arthritis, and osteoarthritis and to eliminate the following immune mediated disorders: insulin dependent diabetes (type I diabetes); systemic lupus erythrematosis; psoriasis; immune pathologies induced by infectious agents, viral infections or bacterial infections; tuberculosis; lepromatous leprosy; transplant rejection; graft versus host disease; atopic conditions; eosinophilia; conjunctivitis and glomerular nephritis. As acknowledged by the Examiner, the specification is enabling for the treatment of immune mediated diseases selected from the group consisting of multiple sclerosis and arthritis. Hence, treatment (and prevention) of multiple sclerosis, rheumatoid arthritis, and osteoarthritis, as defined in the proposed amended claims are deemed to be adequately enabled.

Additionally, apparently the Examiner holds the view that a method of preventing a disease means that such a method provides a cure for the disease. However, the term "preventing" in the present claims refers to prophylactic treatment of the diseases recited therein. For clarification purposes, claim 18 has been amended to change the term "preventing" to prophylactically treating as discussed on page 13, lines 3-4 of the specification.

According to Wikipedia (http://en.wikipedia.org/wiki/Prophylaxis), "prophylaxis", which is Greek for "to guard or prevent beforehand", is defined as any medical or public health procedure whose purpose is to prevent, rather than treat or cure, disease. Roughly, prophylactic measures are divided between *primary* prophylaxis (to prevent the development of a disease) and *secondary* prophylaxis (whereby the disease has already developed and the patient is protected against worsening of this process).

Accordingly, it is the Applicants' position that the present specification provides adequate enablement for both the therapeutic and the prophylactic treatment of multiple sclerosis, rheumatoid arthritis, and osteoarthritis.

For the reasons set forth above and in view of the amendments to claim 18, it is respectfully requested that the rejection of claims 18-28 under 35 U.S.C. §112, first paragraph, as failing to provide an enabling disclosure, be withdrawn.

Rejection under 35 U.S.C. §103(a):

Claims 18-28 are rejected under 35 U.S.C. §103(a) as being unpatentable over United States Publication No. 2002/0183299 A1 to Voskuhl (hereinafter referred to as "Voskuhl") in view of United States Patent No. 5,340,584 to Spicer et al. (hereinafter referred to as "Spicer"). It is the Examiner's position that it would have been obvious to combine the method of Voskuhl for treating multiple sclerosis, which is an autoimmune mediated disease, by administering an estrogenic hormone, such as estriol or a metabolite of estriol in view of the teachings of Spicer. Applicants respectfully traverse this rejection.

Voskuhl teaches a method of treating an autoimmune disease, more specifically Th-1 mediated autoimmune diseases, such as multiple sclerosis, by administering at least one primary agent being an estrogen or estrogen receptor active agent. The examples in the reference describe a study in which women with clinically definite multiple sclerosis were treated with

estriol. Paragraph [0039] of the reference states that the primary agent may also be a metabolite or derivative of E1, E2, or E3 which are active at the estrogen receptor α or β. The reference further states that metabolites and derivatives may have a similar core structure to E1, E2, or E3, but may have one or more different groups, i.e., hydroxyl, ketone, halide, etc., at one or more ring positions. Spicer teaches compositions and methods which are effective to inhibit conception and to treat gynecological disorders, comprising administering a gonadotropin hormone releasing hormone composition and an estrogenic composition. Note col. 7, lines 3-13, of the reference which states: "Natural and synthetic estrogenic compositions which can be used according to the invention described herein include natural estrogenic hormones and congeners, including but not limited to estradiol, estradiol benzoate, estradiol cypionate, estradiol valerate, estrone, diethylestilbestrol, piperazine estrone sulfate, ethinyl estradiol, mestranol, polyestradiol phosphate, estriol, estriol hemisuccinate, quinestrol, estropipate, pinestrol and estrone potassium sulfate. Equine estrogens, such as equilelinin, equilelinin sulfate and estetrol, may also be employed."

According to the Examiner, Voskuhl does not explicitly teach estetrol as a primary agent used in a method of treating or preventing autoimmune mediated disease. However, the Examiner asserts that since Spicer teaches that estriol and estetrol are functionally equivalent natural estrogen hormones that can be used interchangeably, it would have been obvious to employ estetrol in the method of treating or preventing an autoimmune mediated disease taught by Voskuhl. The Examiner additionally states: "Furthermore, if such a species or subgenus is structurally similar to that claimed, such as estriol and estetrol in this instant, its disclosure may motivate one of ordinary skill in the art to choose the claimed species or subgenus from the genus, based on the reasonable expectation that structurally similar species usually have similar properties".

As discussed on pages 4-5 of the present application, available knowledge of the pharmacological properties of estetrol, at the time the present invention was made, clearly shows that estetrol is a much less potent estrogen than the natural estrogens estradiol and estriol. For instance, Levine et al., 1984, Uterine vascular effects of estetrol in nonpregnant ewes, Am. J. Obstet. Gynecol., 148:73, 735-738 observe: "When intravenously administered in nonpregnant ewes, estetrol is 15 to 30 times less potent than estriol and 17β-estradiol in uterine vasodilation".

Indeed, until the date of the present invention, as far as Applicants are aware, there is no record of any actual therapeutic use of estetrol. In a few patent publications (such as Spicer) estetrol is mentioned; however, none of these references actually illustrate the therapeutic use of estetrol.

Consequently, Applicants respectfully traverse the position that one skilled in the art having adequate knowledge in the field of steroids would conclude from Spicer that estriol and estetrol can be used interchangeably. Rather, it is Applicants' position that one having ordinary skill in the art would attach much more relevance to the available scientific literature showing that estetrol has very limited estrogenic activity than to patent publications in which estetrol is presented as an estrogen that may be used in a therapeutic method without there being provided any data to corroborate this "suggestion".

Accordingly, one having ordinary skill in the art would ***not*** be motivated to combine the teachings of Voskuhl with those of Spicer since these references related to very different fields (autoimmune diseases versus contraception and gynecological disorders) and also because a skilled person looking for alternative estrogenic agents besides those explicitly mentioned in Voskuhl would find little guidance in Spicer. In addition, it is Applicants' position that even if a skilled person would try to combine the teachings of Voskuhl with those of Spicer, such skilled person would ***not*** be motivated by Spicer to use estetrol in the method of treating immune diseases described in Voskuhl because this skilled person, based on the available knowledge of estetrol, would not expect that estetrol could successfully be used in such a method. Thus, it is only with the benefit of hindsight that one can argue that a skilled person would have been motivated by Spicer to employ estetrol as the primary agent in the method of treating autoimmune disease of Voskuhl.

For the reasons set forth above, it is respectfully requested that the rejection of claims 18-28 under 35 U.S.C. §103(a) be withdrawn as the combination of Voskuhl with Spicer fails to render these claims obvious.

CONCLUSION

Based on the foregoing amendments and remarks, reconsideration of the rejections and allowance of claims 18-28 are requested.

Respectfully submitted,

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